AMENDMENTS TO THE SPECIFICATION

In the specification at page 7, lines 15-28, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

There have been very few studies that address the "difficult" cyclisation issue. Cavalier-Frontin *et al* (1993) reported on the use of reversible chemical modifications of the peptide backbone to enhance cis-amide conformations. In the synthesis of cyclo-[Phe-Phe-Phe-Phe] (SEQ ID NO:32), each amide N was substituted with a BOC protecting group. The cyclisation yield increased from 1% to 27%. Similarly, the use of the N-(2-hydroxy-4-methoxybenzyl) (Hmb) group as a reversible N-backbone amide substituent has resulted in increases in yield of cyclic peptides (Ehrlich *et al*, 1996). It must be emphasised that here the "auxiliary" is placed on the backbone amide, and not on the N-terminal amine that reacts to form the "difficult" amide bond.

In the specification at page 8, lines 19-24, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Muir *et al* demonstrated that "native" ligation, using a cysteine residue at the N-terminus and a thioester at the C-terminus, can be applied in an intramolecular way to generate cyclic peptides (Camarero and Muir, 1997), as shown in Scheme 5. In Scheme 5, YAVTGRGDSPAASS is SEQ ID NO:33 and cyclo-CYAVTGRGDSPAASSG is SEQ ID NO:34.

In the specification at page 28, lines 28-34, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Figure 1 shows a comparison of the coupling yields for the Fmoc chain-assembly of STA-91(699-709) using: (A) Standard 10

min HBTU coupling protocols (-o-), which resulted in an average coupling yield of 83%; and (B) Hnb-assisted 10 min HBTU coupling protocols, with the incorporation of the Hnb auxiliary at Ile^{707} (-Δ-). Average coupling yield 99.6%. In Figure 1, VSILETKIYGT is SEQ ID NO:35.

In the specification at page 34, lines 4-8, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Example 1 Synthesis of HS-$(CH_2)_2$-Tyr-Arg-Phe-Gly-OH (SEQ ID NO:1)

Synthesis was performed on Fmoc-Gly-WANG resin (0.36 mmol/g). The tetrapeptide Tyr-Arg-Phe-Gly (SEQ ID NO:21) was assembled using stepwise Fmoc-SPPS, with alternating HBTU coupling and piperidine deprotection as follows:

In the specification at page 34, lines 28-36, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The Tyr(Bu)-Arg(PMC)-Phe-Gly-WANG resin (SEQ ID NO:2) (1 g) was then treated with S-(p-methylbenzyl)-2-mercapto-acetaldehyde (58 mg; 0.32 mmol, Bitan *et al*, 1997) dissolved in MeOH/DMF/AcOH (47/47/5) (6 mL). After 5 min stirring 60 mg of $NaBH_3CN$ was added and the mixture left for 60 minutes. The reductive alkylation step was then repeated once more to ensure complete reaction. The resin was washed several times with DMF/MeOH, MeOH/DCM and DCM and finally air dried.

In the specification at page 35, lines 15-18, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Example 2 Synthesis of N-(5-nitro-2-mercaptobenzyl)-Tyr-Arg-Phe-Gly-OH (SEQ ID NO:3)

Tyr(Bu)-Arg(PMC)-Phe-Gly-WANG resin (SEQ ID NO:2) was prepared as described in Example 1.

In the specification at page 35, lines 28-35, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

700 mg of resin was treated with 10 mL TFA/H_2O (95/5) for 1 hour at room temperature. The TFA was removed *in vacuo* and the residue dissolved in HPLC buffers A/B 1/1 (5 mL). The solution was then loaded directly on to an HPLC column and purification of the product performed as in Example 1. 25 mg N-(5-nitro-2-mercaptobenzyl)-Tyr-Arg-Phe-Gly-OH (SEQ ID NO:3) were obtained from lyophilisation (20% yield), Mr 708.4 (calcd for $C_{33}H_{40}N_8O_8S$: 708.27).

In the specification at page 36, lines 1-19, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Example 3 Synthesis of HS-$(CH_2)_2$-Ala-Phe-Leu-Pro-Ala-OH (SEQ ID NO:4)

Ala-Phe-Leu-Pro-Ala-WANG resin (SEQ ID NO:5) was prepared starting from Fmoc-Ala-WANG resin (0.44 mmol/gram) using standard Fmoc-SPPS protocols, with HBTU coupling and piperidine deprotection as described in Example 1. To 500 mg of this resin , a solution of 300 mg *o*-nitrobenzenesulfonylchloride in DMF (4 mL) containing DIEA (200 µL) was added. After 30 minutes, the resin was drained and washed with DMF (3x). The resin was mixed with a solution of S-(p-methylbenzyl)-2-mercaptoethanol (270 mg, 1.5 mmol) in DCM (5mL). Triphenylphosphine (393 mg, 1.5 mmol) and diethylazodicarboxylate (DEAD, 261 mg, 1.5 mmol) were premixed in DCM (5 mL). After 1 minute, the solution was added to the resin and the reaction left for 30 minutes. The resin was washed with DCM (3x) and DMF(3x). The resin was further treated with a solution of NaSPhe (200 mg, 1.5 mmol) in

DMF (4 mL) for 30 minutes. The resin was washed with DMF (3x) and MeOH/DCM (3x) and air dried.

In the specification at page 36, lines 22-28, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

500 mg of resin was cleaved using HF/*p*-cresol/*p*-thiocresol (9/1/1) (10 mL) (1 hour at 0°C) and was worked up as described in Example 1. The crude residue was dissolved in buffers A/B (1/1) and purified on HPLC yielding HS-$(CH_2)_2$-NH-CH(CH_3)-CO-Phe-Leu-Pro-Ala-OH (SEQ ID NO:6) (25 mg, 22% yield). Mr : 577.1 (calc for $C_{28}H_{43}N_5O_6S$: 577.29)

In the specification, from page 36, line 30 to page 37, line 8, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Example 4 Synthesis of N-(2-hydroxy-5-nitrobenzyl)-Ala-Phe-Leu-Pro-Ala-OH (SEQ ID NO:7)

Fmoc-Ala-trityl resin (0.4mmol/gr) was first prepared from trityl resin (0.96 mmol/gr) using protocols provided by Pepchem (Tubingen, Germany). Ala-Phe-Leu-Pro-Ala-Trityl resin (SEQ ID NO:36) was assembled using standard Fmoc SPPS protocols, as in Example 1. This resin (0.5 gr) was further treated with a solution of 2-hydroxy-5-nitrobenzaldehyde (115 mg, 0.7 mmol) and AcOH (20 µL) in DMF (2 mL). After 5 minutes the resin was drained and a second aldehyde treatment was performed. The resin was drained, and washed copiously with DMF until eluent was colourless. A solution of $NaBH_4$ (150 mg, 4 mmol) in DMF/MeOH 3/1 (4 mL) was added and the resin stirred for 10 minutes. The resin was drained, washed with DMF/MeOH 1/1, DCM/MeOH 1/1 and DCM and air dried.

In the specification at page 37, lines 11-19, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The resin was treated with DCM (10mL) and TFA (100 µL) for 1 hour. The solution was evaporated, buffer B (3 mL) was added and the resin filtered off. The solution was loaded directly on to a preparative HPLC column and HPLC purification performed using a 2% gradient (from 90% A to 10% A in 40 minutes). After lyophilisation N-(2-hydroxy-5-nitrobenzyl)-Ala-Phe-Leu-Pro-Ala-OH (SEQ ID NO:7) (114 mg) was isolated as a white powder (85% yield), Mr: 668.2 (calcd for $C_{33}H_{44}N_6O_9$: 668.32).

In the specification at page 37, lines 21-28, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Example 5 Synthesis of N-(2-hydroxy-6-nitrobenzyl)-Ala-Phe-Leu-Pro-Ala-OH (SEQ ID NO:8)

The linear peptide was synthesised on trityl resin as described in example 4, but employing 2-hydroxy-6-nitrobenzaldehyde (Harayama *et al*, 1994). After lyophilisation N-(2-hydroxy-6-nitrobenzyl)-Ala-Phe-Leu-Pro-Ala-OH (SEQ ID NO:8) (85 mg) was isolated as a white powder (63% yield), Mr 668.2, calcd for $C_{33}H_{44}N_6O_9$: 668.32).

In the specification at page 48, lines 2-18, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

To determine if the activating effect of the nitro substituent could also improve acyl transfer rates and yields with more sterically demanding residues a second set of acylation experiments were carried out. In these experiments, the same auxiliaries were each introduced onto the resin-bound tetrapeptide, Val-Ala-Gly-Phe (SEQ ID NO:9), by reductive

alkylation and subjected to acylation by HBTU-activated Fmoc-Gly, Fmoc-Phe and Fmoc-Val. Due to the inherent difficulty associated with the acylation of sterically hindered secondary amines the acyl transfer reaction time course in these experiments was increased to 1, 6, and 24 h. Following acylation, the peptide-resins were subjected to piperidine base treatment to exclusively observe the N^{α}-amino acylation products and then cleaved with 0.5% TFA in DCM for 30 min. The products were identified by ES-MS or LC/MS analysis and quantified by RP-HPLC peak integration. The results are summarised in Table 3.

In the specification at page 49, lines 3-4, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Distribution of N^{α}-acylation products on the Val-Ala-Gly-Phe (SEQ ID NO:9) sequence by N^{α}-auxiliary directed $O \rightarrow N$ acyl migration.

In the specification at page 51, lines 18-36, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Acylation Experiments. The Ala-Gly-Phe and Val-Ala-Gly-Phe (SEQ ID NO:9) sequences were assembled on chlorotrityl resin (0.96 mmol/g, PepChem) using standard Fmoc/HBTU protocols. The resin was then divided into three portions in separate reaction vessels, and swollen in DMF for 10 min. Three equiv of Fmoc-protected glycine, alanine, phenylalanine, and valine were coupled to Ala-Gly-Phe-resin or Val-Ala-Gly-Phe-resin (SEQ ID NO:37) using 2.95 equiv of 0.5 M HBTU in DMF with 4 equiv of DIEA for 1, 10, and 60 min or 1, 6, and 24 h, respectively. To examine N^{α}-acylation exclusively and also remove Fmoc groups, resins samples before cleavage were subjected to 2 cycles of 5 min piperidine/DMF (1:1) and 5 min DMF/piperidine/H_2O (4:4:2) treatments, then dried with DCM:MeOH (1:1). Trityl resin samples were cleaved with 0.5% TFA in DCM for 30 min. The TFA

cleavage solutions were evaporated with a stream of nitrogen, and the product dissolved in 100 µL of 50% buffer B. Samples were centrifuged, supernatant collected, then immediately analysed by RP-HPLC and ES-MS or LC/MS.

In the specification at page 52, lines 3-16, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

In principle, the 2,6-Hnb and Hmb groups should have a similar effect on disrupting hydrogen-bonding networks, since they both alter the backbone structure of growing peptide chains and remove a backbone hydrogen-bond donor. To demonstrate this beneficial effect, the STAT-91(699-709) sequence, TGYIKTELISV (SEQ ID NO:38), which we have previously reported as "difficult" in both Fmoc- and Boc-SPPS (Meutermans et al 1996; Alewood et al, 1997), was assembled using standard chain assembly protocols and also with the assistance of *N*-Hnb backbone substitution under identical experimental conditions. The STAT-91 peptide was selected because it does not contain a relatively unhindered site before the "difficult" section is encountered, and thus precludes the use of the Hmb auxiliary.

In the specification at page 55, lines 10-22, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Example 9: Synthesis of a difficult cyclic peptide, Ala-Phe-Leu-Pro-Ala (SEQ ID NO:10).:

H-Ala-Phe-Leu-Pro-Ala-OH (SEQ ID NO:39) was a recently reported example of a sequence which is difficult to cyclise (Schmidt and Langner, 1997). When subjected to cyclisation conditions, dimer and higher oligmers were generated, but no target cyclopentapeptide was formed. We have employed this linear peptide to probe our methodology and compare it with the prior art methods. In the following set of experiments we

demonstrate that this Ala-Ala amide bond in the monocycle was not accessible from this linear peptide using prior art methodologies, but was accessible using our photolabile auxiliaries.

In the specification at page 56, lines 2-8, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Cyclisation of unsubstituted Ala-Phe-Leu-Pro-Ala (SEQ ID NO:19). As a control experiment we attempted to cyclise the unsubstituted linear peptide (Ala-Phe-Leu-Pro-Ala) (SEQ ID NO:19) using standard cyclisation conditions (1mM in DMF, 3eq. BOP, 5eq. DIEA, 3h at rt). As expected from the previously reported results, only cyclic dimer and some trimer were obtained, but no target monocyclic product.

In the specification at page 56, lines 11-14, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

We initially evaluated an ethanethiol auxiliary. This auxiliary was introduced *via* an on-resin Fukuyama synthesis as described in Example 3, using the reaction sequence summarized in Scheme 12, wherein Ala-Phe-Leu-Pro-Ala is SEQ ID NO:19.

In the specification at page 58, lines 9-13, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Scheme 13: Cyclisation of auxiliary containing peptides **4,5** (A) and formation of the target cyclic peptides **10,11** (B) ; i) 3 eq. BOP / 5 eq. DIEA, 3h at rt; ii) 1 eq. BOP / 2 eq. DIEA, 3h rt; 10 eq. DIEA, 12h rt or 1h at 65°C; iii) hν(366nm), wherein Ala-Phe-Leu-Pro-Ala is SEQ ID NO:19 and Phe-Leu-Pro-Ala-Ala is SEQ ID NO:31.

In the specification at page 60, lines 1-3, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Similarly *N*-(6-nitro-2-hydroxybenzyl)Phe-Leu-Pro-Ala-Ala (SEQ ID NO:11) 5c was assembled and cyclised as above. The all-L cyclo pentapeptide **11c** was isolated in 45% yield.

In the specification at page 60, lines 13-19, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The cyclic product was characterised by chiral amino acid analysis and ^{1}H NMR. The spectral data were in good agreement with the reported data. Furthermore, an independent sample of cyclic peptide, prepared from the cyclisation of Phe-Leu-Pro-Ala-Ala (SEQ ID NO:31) according to Schmidt *et al* (1997) coeluted with the product obtained from photolysis.

In the specification at page 61, lines 9-22, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Cyclo-[S-$(CH_2)_2$-Ala-Phe-Leu-Pro-Ala] (SEQ ID NO:12) 2. Cyclisation of HS-$(CH_2)_2$-Ala-Phe-Leu-Pro-Ala (SEQ ID NO:13) **1** (10 mg of the TFA salt, 0.014 mmol) produced the monocyclic thioester **2** (3.4 mg, 45% yield): Mr: 559.3, calcd for $C_{28}H_{41}N_5O_5S$: 559.3. The thioester was hydrolysed using aqueous ammonium bicarbonate buffer (0.1 M, pH 8, 6h at 60 °C) to form the *C*-terminal amides and acids. Under the mild base conditions these thiol-products oxidised to the disulfides **3** which were characterised by ES-MS. [S-$(CH_2)_2$-NH-CH(CH_3)-CO-Phe-Leu-Pro-Ala-NH_2]$_2$ (SEQ ID NO:40) Mr: 1150.8, calcd for $C_{56}H_{86}N_{12}O_{10}S_2$: 1150.6, [S-$(CH_2)_2$-NH-CH(CH_3)-CO-Phe-Leu-Pro-Ala-NH_2]-S-$(CH_2)_2$-NH-CH(CH_3)-CO-Phe-Leu-Pro-Ala-OH (SEQ ID NO:14) Mr: 1151.8, calcd

for $C_{56}H_{85}N_{11}O_{11}S_2$: 1151.6, [S-$(CH_2)_2$-NH-CH$(CH_3)$-CO-Phe-Leu-Pro-Ala-OH]$_2$ (SEQ ID NO:41) Mr: 1152.8, calcd for $C_{56}H_{84}N_{10}O_{12}S_2$: 1152.6.

In the specification, from page 61, line 24 to page 62, line 12, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Cyclo-[*N*-(5-nitro-2-hydroxybenzyl)-Ala-Phe-Leu-Pro-Ala] (SEQ ID NO:42) (10a). Cyclisation of *N*-(5-nitro-2-hydroxybenzyl)-Ala-Phe-Leu-Pro-Ala (SEQ ID NO:15) **4a** (30 mg of the TFA salt, 0.038 mmol), produced **10a** (12.5 mg, 0.019 mmol) in 51% yield : ES-MS *Mr* 650.2, calcd for $C_{33}H_{42}N_6O_8$, 650.3 (monoisotopic). ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 11.5 (s, 1H, OH), 8.40 (d, 1H, N*H*$_{Leu}$), 8.02 (dxd, 1H, *H*-ar), 7.70 (d, 1H, *H*-ar), 7.4 (d, 1H, *H*N$_{Phe}$), 7.20-7.30 (m, 5H, *H*-Phe), 6.99 (d, 1H, *H*-ar), 6.54 (d, 1H, *H*-N$_{Ala}$), 5.00 (s, 1H, ArCH*h*N-), 4.91 (m, 1H, α-Ala^5), 4.75 (q, 1H, α-Ala^1), 4.59 (m, 1H, α-Phe), 4.50 (m, 1H, α-Leu), 4.27 (t, 1H, α-Pro), 3.88 (d, 1H, ArCH*h*N-), 3.62 (m, 1H, δ-Pro), 3.37 (m, 1H, δ-Pro), 2.97 (m, 1H, β-Phe), 2.82 (m, 1H, β-Phe), 2.04 (m, 2H, β-Pro), 1.88 (m, 1H, γ-Pro), 1.73 (m, 1H, β-Leu), 1.65 (m, 1H, γ-Pro), 1.44 (m, 1H, γ-Leu), 1.33 (m, 1H, ß-Leu), 1.24 (d, 3H, β-Ala^5), 0.91 (d, 3H, β-Ala^1), 0.85 (m, 6H, δ-Leu). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 172.61, 170.34, 170.07, 169.95, 169.47, 160.40, 139.73, 136.88, 129.31, 128.14, 126.50, 125.72, 124.21, 122.65, 115.00, 61.04, 56.50, 55.74, 48.70, 46.31, 44.34, 41.37, 38.28, 31.30, 24.20, 22.81, 22.68, 21.17, 18.97, 15.35.

In the specification at page 62, lines 14-23, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Cyclo-[*N*-(6-nitro-2-hydroxybenzyl)-Ala-Phe-Leu-Pro-Ala] (SEQ ID NO:16) (11a). From cyclisation of *N*-(6-nitro-2-hydroxybenzyl)-Ala-Phe-Leu-Pro-Ala (SEQ ID NO:43) **5a** (20 mg of the TFA salt, 0.025 mmol), **11a** (6.5 mg, 0.010 mmol) was obtained in 39% yield

: ES-MS *Mr* 650.6, calcd for $C_{33}H_{42}N_6O_8$: 650.3 (monoisotopic). ^{13}C NMR (75 MHz, CD_3OD, ppm) δ 178.07, 176.95, 174.54, 174.32, 173.72, 159.11, 153.19, 140.41, 131.99, 129.96, 129.54, 127.57, 121.18, 116.57, 62.75, 60.67, 58.55, 54.05, 51.15, 44.54, 43.41, 34.85, 33.67, 25.03, 24.13, 22.30, 21.31, 15.49, 13.89.

In the specification, from page 62, line 25 to page 63, line 2, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Cyclo-[*N*-(6-nitro-2-hydroxybenzyl)-Phe-Leu-Pro-Ala-Ala] (SEQ ID NO:17) (11c). From cyclisation of the *N*-(6-nitro-2-hydroxybenzyl)-Phe-Leu-Pro-Ala-Ala (SEQ ID NO:18) (20 mg of the TFA salt, 0.025 mmol), **11a** (7.3 mg, 0.011 mmol) was obtained in 44% yield : ES-MS *Mr* 650.2, calcd for $C_{33}H_{42}N_6O_8$: 650.3 (monoisotopic). ^{13}C NMR (75 MHz, DMSO-d6, ppm) δ 171.43, 171.00, 169.46, 167.56, 156.65, 138.43, 129.24, 129.05, 128.32, 128.18, 126.08, 119.50, 115.87, 114.60, 62.18, 60.69, 51.07, 49.38, 46.57, 45.46, 41.54,38.17, 33.65, 31.43, 24.37, 22.73, 22.32, 21.06, 17.87, 16.92.

In the specification, at page 63, lines 4-19, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Cyclo-[Ala-Phe-Leu-Pro-Ala] (SEQ ID NO:10) (12a). a) Cyclo-[*N*-(6-nitro-2-hydroxybenzyl)-Ala-Phe-Leu-Pro-Ala] (SEQ ID NO:16) (1mM MeOH) was purged with nitrogen for 30 minutes and then photolysed with a standard laboratory UV lamp (366nm, 0.25A) for three hours. The MeOH was evaporated and residue dissolved in 50% buffer B and the solution loaded directly onto a Vydac C18 column (preparative) for HPLC purification. Cyclo-[Ala-Phe-Leu-Pro-Ala] (SEQ ID NO:10) was isolated in 52% yield. The product coeluted with a independently synthesised sample. ES-MS *Mr* 499.4, calcd for $C_{26}H_{37}N_5O_5$, 499.3 (monoisotopic).

b) Photolysis of purified cyclo-[*N*-(6-nitro-2-hydroxybenzyl)-Phe-Leu-Pro-Ala-Ala] (SEQ ID NO:17) was perfomed as described above. Cyclo-[Phe-Leu-Pro-Ala-Ala] (SEQ ID NO:20) was isolated in 28% yield. The product coeluted with a independently synthesised sample. ES-MS *Mr* 499.1, calcd for $C_{26}H_{37}N_5O_5$, 499.3 (monoisotopic).

In the specification, at page 63, lines 21-33, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Example 10: Application of the photolabile auxiliary for the cyclisation of an all-L-tetrapeptide, Tyr-Arg-Phe-Gly (SEQ ID NO:21), via a ring contraction approach.

We decided to investigate the feasibility of our auxiliary approach for the synthesis of a more constrained all-L cyclo tetrapeptide. Standard cyclisation of the linear peptide Tyr-Arg-Phe-Gly (SEQ ID NO:21) yields cyclic monomer / cyclic dimer / cyclic trimer in a ratio of 2 / 8 / 3 . Cyclisation of (HnB)Tyr-Arg-Phe-Gly (SEQ ID NO:22) was performed as described before, but heating (65°C after DIEA addition) was continued for 20 hours (instead of 1h). The product cyclo-[(HnB)Tyr-Arg-Phe-Gly] (SEQ ID NO:23) was isolated in 40% yield.

In the specification, at page 64, lines 1-5, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Photolysis of this product in MeOH/AcOH was slow and yielded impure cyclo[Tyr-Arg-Phe-Gly] (SEQ ID NO:24), whereas photolysis in THF, DMF or Dioxane was significantly faster (complete in 1 hour). The cyclo-[Tyr-Arg-Phe-Gly] (SEQ ID NO:24) was isolated in 41 % yield (photol. step).

In the specification at page 64, lines 20-27, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The first peptide segments (peptide 1; GAGPA is SEQ ID NO:26 and AARHT is SEQ ID NO:29) are assembled using standard *in situ* neutralisation protocols and the auxiliary is introduced as described in Examples 1 to 5. Standard HF cleavage and side chain deprotection provides the first unprotected peptide segment. The second peptide segments (peptide 2; LYRAG is SEQ ID NO:25 and LYRAF is SEQ ID NO:28), containing a thiophenylester at the C-terminus, are synthesised as described before (Canne *et al*, 1996).

In the specification at page 65, lines 1-9, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

To optimise the ligation conditions the following experiments are then performed : peptide 1 and peptide 2 are dissolved in DMF at 1 mM, 10 mM and 100 mM concentration and 2 or 5 equivalents of DIEA added. Progress of the reaction is monitored for each experiment by HPLC and LCMS analysis at different time intervals. Several other solvent systems are tested, such as DMSO/DIEA, and aqueous buffers (pH ranging from 4 to 8) (no DIEA). The products are LYRAGGAGPA (SEQ ID NO:27) and LYRAFAARHT (SEQ ID NO:30).

In the specification at page 65, lines 12-15, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

In this experiment we illustrate how we accommodate photolabile backbone linking using this auxiliary approach for the solid phase synthesis of cyclic peptides. Cyclo-FLPAA is SEQ ID NO:20.

In the specification at page 65, lines 19-31, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

2,3-dihydroxy-6-nitrobenzaldehyde (Perez *et al*, 1992) is treated with 1 equivalent bromovaleric acid and 1 equivalent $KHCO_3$ in acetone. The resulting acid is linked to aminomethylated polystyrene. Alanine allyl ester is attached to the resin by reductive amination and the resulting secondary amine acylated with Boc-Ala-OH as described in Example 6. The linear peptide (Phe-leu-Pro-Ala-Ala) (SEQ ID NO:31) is further assembled using *in situ* neutralisation protocols. The N-terminus is deprotected with TFA and the C-terminal allyl protection group removed using $Pd[P(Ph)_3]_4$ as described. The cyclisation is then performed with BOP/DIEA in DMF and the product cleaved from the resin by photolysis.

At the end of the specification, please insert the enclosed 14 pages of sequence listing.

RESPONSE

The Office has entered a sequence listing requirement in the above-referenced application. Applicants enclose a sequence listing diskette, paper copies of the sequence listing and the required statements.

Amendments to the specification are also being made in regard to the sequence identifiers. The amendments are made solely to conform the specification to the enclosed sequence listing and are fully supported by the original application do not constitute new matter. The amendments to the specification comply with the revisions to 37 C.F.R. § 1.121, and separate exhibits are no longer necessary.

This is a complete response to the referenced Notice. The present application is in compliance with the sequence listings requirements. The response is timely filed in light of the enclosed Request for Extension of Time and appropriate fee. No additional fees are required. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be deemed necessary, Applicants respectfully request a telephone call to the undersigned representative to discuss deduction from Applicants' representatives' Deposit Account No. 50-0786/4050.001100.

Should the Office have any questions, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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